Evaluating the concept of a dilution bottle to increase the use of magnesium sulfate for the treatment of severe preeclampsia/eclampsia

Final report

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Contents

Acronyms and abbreviations

FGD	focus group discussion
IDI	in-depth interview
IM	intramuscular
IV	intravenous
$MgSO_4$	magnesium sulfate
NEML	national Essential Medicines List
PE/E	preeclampsia/eclampsia
PVC	polyvinyl chloride
USAID	United States Agency for International Development
USP	United States Pharmacopeial Convention
WFI	water for injection
WHO	World Health Organization

Executive summary

PATH developed the innovative concept of a dilution bottle for delivery of magnesium sulfate ($MgSO_4$) for the treatment of severe preeclampsia/eclampsia (PE/E). This dilution bottle contains 10mL of 50% $MgSO_4$ solution and is marked with a fill line that indicates the fill volume at 25mL. When 50% $MgSO_4$ solution is required, the necessary amount can be withdrawn directly from the bottle. When 20% $MgSO_4$ solution is required, a medical professional can add sterile water (diluent) to the bottle up to the 25mL fill line, which then makes a 20% $MgSO_4$ solution. In theory, this dilution bottle makes it easier to dilute $MgSO_4$ and thus facilitates safe use of the current World Health Organization (WHO) regimen. It also reduces the burden associated with procurement and inventory control, since only one type of dilution bottle needs to be procured and stocked for treatment of PE/E.

Using HealthTech skunkworks funding, we evaluated the technical feasibility, commercial viability, and user acceptability of the $MgSO_4$ dilution bottle through desk research and interviews. To determine user acceptability of the $MgSO_4$ dilution bottle, we leveraged a field evaluation that had been planned for $MgSO_4$ ready-to-use packs. Since the $MgSO_4$ dilution bottle can be provided as a component of the ready-to-use packs, we evaluated acceptability by including it in the packs. The following factors were the particular focus of this evaluation:

Technical feasibility

- Headspace required in the dilution bottle to enable smooth withdrawal of the $MgSO_4$ solution from the bottle.
- The composition material of the dilution bottle to ensure that the fill line mark was clearly visible.

Commercial feasibility

- Primary container listed in national Essential Medicines Lists (NEMLs).
- Policy and regulatory environments that could affect the introduction of the dilution bottle.
- The product cost of the dilution bottle.

User acceptability

- User perception regarding ease of withdrawing the correct amount of MgSO4 solution by syringe.
- User perception regarding expected wastage (the dilution bottle makes 25mL of 20% $MgSO_4$ solution, while the intravenous (IV) loading dose only requires 20mL of 20% $MgSO_4$ solution, which results in 5mL of wastage).

In regard to technical feasibility, our desk research found that the bottle size must be a minimum of 75mL, including headspace, to avoid excess internal pressure. The materials used for the bottles presented some challenges. Although Type I glass is both common and readily available, considering the large size required for the dilution bottles, ease of distribution could be an issue. Polyolefin polymers could alleviate this issue and they are also compatible with $MgSO_4$. However, use of plastics for bottle containers is somewhat unique, and costs might be higher.

In regard to commercial feasibility, our NEML review confirmed that it is unlikely that any of the current NEMLs present a significant hurdle for introduction of a dilution bottle for $MgSO_4$ that contains a 50% concentration of $MgSO_4$ for treatment of PE/E. Most sub-Saharan African and South Asian countries already list 50% $MgSO_4$ as an anticonvulsant, an antiepileptic, or treatment for PE/E, and only a few countries specify the precise type of primary container.

However, our desk research and an interview with one manufacturer confirmed that a 75mL bottle, which would be the minimum size required for the $MgSO_4$ dilution bottle, is a non-standard size for the pharmaceutical industry. This same manufacturer said that producing a non-standard size bottle could have implications for production costs and time to market, since manufacturers would need to identify a source for the non-standard size bottles, modify their production lines, and then obtain regulatory approval.

In regard to user acceptability, our field evaluation of the dilution bottle concept revealed that health care professionals do not appreciate or value the dilution bottle as much as we had expected. The process of diluting and withdrawing the correct amount was perceived to be complex and time consuming. In addition, they were concerned about the product wastage that would result. Finally, these health care professionals were concerned that someone might mistakenly withdraw an incorrect volume or overfill the bottle by mistake.

Due to the several issues we uncovered with technical feasibility, commercial feasibility, and user acceptability, we recommend termination of any further development of a dilution bottle.

Despite our findings and conclusions about development of the dilution bottle, our field evaluation found that health care professionals would actually prefer having a 20% $MgSO_4$ solution, since such a solution would obviate potential mistakes in dilution and would facilitate timely treatment of women with PE/E. Unfortunately, our NEML review ascertained that a 20% concentration of $MgSO_4$ is rarely listed on NEMLs, and changing NEMLs to include a 20% $MgSO_4$ solution would require substantial time and effort. Furthermore, it would be difficult to incentivize manufacturers to produce and supply a 20% $MgSO_4$ solution, since the market size for this critical medicine remains relatively small.

This unmet need for a 20% $MgSO_4$ solution to treat PE/E does not appear to have an easy solution. The most important factor to be considered is whether the impact of not having a 20% $MgSO_4$ solution is significant or not. If the lack of a 20% $MgSO_4$ solution frequently leads to serious adverse events, such as loss of life due to non-timely or improper treatment of severe PE/E, then the cost and effort of changing NEMLs as well as financially motivating manufacturers to produce a 20% $MgSO_4$ solution might be justified. Alternatively, PATH might consider providing alternatives to a 20% $MgSO_4$ solution, such as developing a simplified regimen that would not require health care professionals to make dilutions at time of administration.

Background

PATH developed the concept of a dilution bottle (Figure 1) for delivery of magnesium sulfate ($MgSO_4$) for the treatment of severe preeclampsia/eclampsia (PE/E). This dilution bottle contains 10mL of 50% $MgSO_4$ solution and is furnished with a rubber septum that self-seals after needle insertion. The volume of the bottle itself is at least 30mL. It is marked with a fill line that indicates the fill volume at 25mL. When 50% $MgSO_4$ solution is required, the necessary amount can be withdrawn directly from the bottle. When 20% $MgSO_4$ solution is required, a medical professional can add sterile water (diluent) to the bottle up to the 25mL fill line, which then makes a 20% $MgSO_4$ solution. After mixing, the necessary amount of the 20% solution can then be withdrawn. This dilution bottle provides several benefits for supplying and administering the current World Health Organization (WHO) regimen:

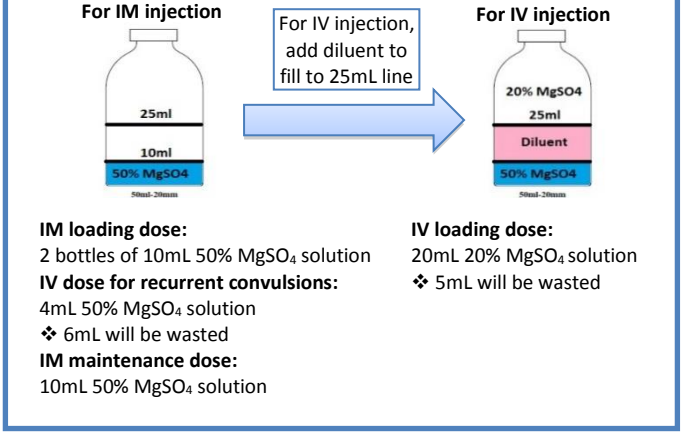

Figure 1. Dilution bottle conceptual design for intramuscular (IM) and intravenous (IV) injection.

- It encourages health care professionals to use $MgSO_4$ since they are currently unwilling to use it due to a complex dilution process required to make a 20% solution.
- It facilitates safe use of the recommended treatment regimen (see Box 1) by obviating the need for remembering complex equations for dilution, thus eliminating the chance that the wrong dilution might be administered. If the dilution bottle is dedicated to the treatment of severe preeclampsia/eclampsia (PE/E), it minimizes confusion about which $MgSO_4$ product to use when a woman presents with severe PE/E.
- It reduces the burden associated with procurement and inventory control, since only one type of dilution bottle needs to be procured and stocked for treatment of PE/E.
- It could further accelerate the use of the recommended regimen if it were provided together with other necessary items, such as a large syringe. (PATH's work for Recommendation 10 under the UN Commission on Life-Saving Commodities for Women and Children identified the necessary items that users prefer using with $MgSO_4$.)

Objectives

HealthTech skunkworks funding was used to ascertain the technical feasibility, commercial viability, and user acceptability of the $MgSO_4$ dilution bottle in order to determine how we should best proceed.

Technical feasibility

Vials with rubber septa are commonly available and often utilized as containers for sterile pharmaceutical products that require a complete seal, such as vaccines that require reconstitution. However, it was unclear how much headspace would be required in the dilution bottle to enable smooth withdrawal of $MgSO_4$ solution from the bottle. In addition, the composition material of the dilution bottle required further investigation to ensure that the fill line mark was clearly visible.

Commercial feasibility

Some national Essential Medicines Lists (NEMLs) contain information regarding the primary container, which might create a hurdle for product introduction. Policy and regulatory environments had to be investigated. Furthermore, the product cost of the dilution bottle had to be estimated. Since $MgSO_4$ is such an inexpensive drug, the cost of its packaging should not be a factor that otherwise might deter its use.

User acceptability

Although our proposed dilution bottle would simplify the administration of $MgSO_4$ solution, user acceptability was uncertain. Specifically, we sought to investigate how users would perceive the fact that they would need to withdraw the correct amount of $MgSO_4$ solution by syringe for both the intravenous (IV) loading dose and the IV dose for recurrent convulsions, and that some product wastage had to be expected with these two doses (Figure 1).

Methods

We utilized desk research and an interview with one manufacturer to identify the technical and commercial feasibilities for the $MgSO_4$ dilution bottle.

In order to determine user acceptability of the $MgSO_4$ dilution bottle, we leveraged a field evaluation that had been planned for the $MgSO_4$ ready-to-use packs. Since the $MgSO_4$ dilution bottle can be provided as a component of the ready-to-use packs, we evaluated acceptability by including it in the ready-to-use packs. This work was funded through UNICEF/UNCoLSC.

This field evaluation was conducted through focus group discussions (FGDs) and several in-depth interviews (IDIs) with health care professionals (i.e., Ob/Gyns and midwives), policymakers, key opinion leaders, and procurement personnel in Ethiopia and Uganda in January 2015.

In both FGDs and IDIs, three configurations of ready-to-use mock-up packs, created using PATH's 3D printer, were shown to participants and interviewees, one at a time, in order for them to visualize the contents of the packs and easily understand the advantages and disadvantages of each pack configuration. In addition, a video that PATH developed was shown to demonstrate the use of the dilution bottles.

Two of the three pack configurations contained mock-ups for the two different types of dilution bottles (Box 1). Although we initially started with the dilution bottle containing a 50% $MgSO_4$ solution (the $MgSO_4$ dilution bottle), our discussion with the manufacturer of $MgSO_4$ made us realize that the dilution bottle could alternatively contain water for injection (WFI) such that users could add an amount of 50% $MgSO_4$ solution to WFI in the bottle when a 20% solution is required. As a result, we tested both types of dilution bottles in

Box 1. Two types of dilution bottles

$MgSO_4$ dilution bottle (shown in Figure 1) contains 10mL of 50% $MgSO_4$ and is pre-marked with a fill line at 25mL. When a 20% $MgSO_4$ solution is required, the health care professional can simply add WFI to the bottle up to the pre-marked fill line to make a 20% $MgSO_4$ solution. Then, 20mL can be withdrawn from the 25mL $MgSO_4$ solution for the IV loading dose. A small amount (5mL) of $MgSO_4$ will remain unused. (When 50% $MgSO_4$ is required, the entire amount of the 50% solution can be withdrawn directly from the bottle for administration.)

WFI dilution bottle contains 12mL of WFI and is pre-marked with a fill line at 20mL. When 20% $MgSO_4$ solution is required, the health care professional can add 8mL of 50% $MgSO_4$ solution up to that fill line and then withdraw all of the resulting 20mL solution from the bottle. Since 50% $MgSO_4$ solution is typically procured in 5g in 10mL ampules/vials, adding 8mL of 50% $MgSO_4$ to this dilution bottle results in 2mL of unused 50% $MgSO_4$ solution remaining in the ampule/vial.

the field evaluation.

Summary findings

Technical feasibility: Appropriate specifications for the dilution bottle

Box 2 lists specifications for the $MgSO_4$ dilution bottle that were identified based on desk research.

The $MgSO_4$ dilution bottle contains 10mL of 50% $MgSO_4$ solution. Users are required to add 15mL of WFI to create 25mL of 20% $MgSO_4$ solution and then to withdraw only 20mL of 20% solution. The $MgSO_4$ dilution bottle therefore should be sealed with a sterile, multi-use septum such that the contents of the bottle maintain sterility following multiple needle insertions required for adding WFI and withdrawing the diluted solution.

In addition, adding WFI to the bottle increases the pressure inside the bottle and withdrawing the 20% solution decreases the internal pressure. The difference in this internal pressure would be lower if using larger-volume bottles. A lower internal pressure in turn would make it easier for users to withdraw the contents of the bottle. Our desk research suggests that the contents of the bottle should be less than 35% of the total bottle capacity,[*] which would require a $MgSO_4$ dilution bottle with a capacity greater than 71mL. If a 71mL bottle is utilized, adding 15mL diluent will increase the internal pressure by approximately 32%, resulting in an excess internal pressure of 4.8 psi. Withdrawing 20mL of 20% solution would reduce the internal pressure to –1.1 psi at normal atmospheric pressure. This difference in the internal pressure would allow users to easily withdraw a 20% solution.

However, injectable pharmaceutical products must have ample volume to ensure complete withdrawal of a therapeutic dose from a container. Guidelines state that 0.5mL must be added for a labeled volume of 10mL for a mobile liquid (5% ample volume). Therefore, the $MgSO_4$ dilution bottle should initially contain 10.5mL of 50% $MgSO_4$, and the final volume of the 20% $MgSO_4$ solution should be 26.25mL (25mL x 1.05). This final volume of 26.25mL will push up the bottle size to be a minimum of 75mL to avoid excess internal pressure.

Additionally, the United States Pharmacopeial Convention's (USP) monograph for injectable $MgSO_4$ allows for a ±7% dose variation. Assuming that manufacturers have tight control over their process when making a 50% $MgSO_4$ solution, the final volume of a 20% $MgSO_4$ solution should be between 24.53mL and 28.23mL (Table 3). As mentioned, the final volume of a 20% $MgSO_4$ solution should be 26.25mL, which is well within the ±7% tolerance range, and the fill line should be placed at this level. This will allow sufficient leeway for the width of the fill line, which determines how much WFI users must add to make a 20% solution.

Box 2. $MgSO_4$ dilution bottle specifications based on desk research

- Sealed with a sterile, multi-use septum.
- Total bottle capacity of at least 75mL.
- An initial fill of 10.5mL 50% $MgSO_4$.
- Pre-marked fill line indicating a total fill volume of 26.25mL for the 20% dilution. (Concentration should be ±7% or between 18.6% and 21.4%.)
- Transparent enough to ensure that any particulates can be observed.
- Type I glass or a semi-rigid polyolefin polymer (polyethylene, polypropylene, cyclic polyolefin polymer).

[*] DeGrazio, FL. Closure and Container Considerations in Lyophilization. In: Rey L and May, JC eds. *Freeze Drying/Lyophilization of Pharmaceutical and Biological Products.* 3rd ed. New York, NY: Informa Healthcare; 2010.

Table 3. Tolerance concentration and fill volume for a 20% $MgSO_4$ solution

	50% $MgSO_4$ solution initially included in the dilution bottles			20% $MgSO_4$ solution diluted from a 50% solution			
	Concentration	$MgSO_4$	Total volume	USP required concentration (±7%)	Concentration	$MgSO_4$	Total volume
Low end	50%	5.25g	10.5mL	93%	18.6%	5.25g	28.23mL
Base	50%	5.25g	10.5mL	100%	20.0%	5.25g	26.25mL
High end	50%	5.25g	10.5mL	107%	21.4%	5.25g	24.53mL

The United States Food and Drug Administration recommends that parenteral drugs be contained in Type I glass containers,[†] but certain parenteral drugs can be packaged in plastic containers that "meet the requirements for biological tests and physicochemical tests in the section Test Methods" of the USP monograph.[‡] In addition, containers for parenteral drugs must be transparent to verify that no particulates are in the product. The packaging must be compatible with the drug product.

Our desk research identified that plastic bottles have many benefits over glass. Currently, Type I glass bottles appropriate for parenteral drugs are available with volumes of 50mL, 60mL, and 100mL. A 75mL bottle is uncommon; therefore, expensive, custom manufacturing would likely be required. By contrast, even if custom manufacturing were required for plastic bottles, the cost would likely be much lower. In addition, a custom plastic bottle could be designed to incorporate an embossed fill line that would have greater consistency (and simpler manufacturing) than a line added to existing bottles. Furthermore, plastic bottles would be more resistant to breakage and would be able to yield to the pressures involved in the dilution and removal of a large volume of solution.

Two potential plastic polymers that could be used for the container for MgSO4 are Polyvinyl chloride (PVC or polylefin plastic polymers. PVC and polyolefin plastic polymers have been used for parenteral pharmaceutical products. PVC is a flexible, non-rigid polymer and is often used for IV bags. However, using PVC as a container for $MgSO_4$ should be avoided due to issues associated with manufacturing, filling, and storing. Polyolefin polymers (e.g., polyethylene, polypropylene, and cyclic olefin polymers) are semi-rigid, transparent, and compatible with 50% $MgSO_4$.[§] They are also the most frequently cited hard plastic materials used as containers for liquid parenteral products.

Commercialization feasibility: NEML listing and its implications

Some NEMLs may contain information regarding the primary container (ampule, vial, etc.), which might create a hurdle for introducing $MgSO_4$ in the dilution bottle and might require additional effort to change NEMLs. The WHO website (http://www.who.int/selection_medicines/country_lists/en/), posts NEMLs from various countries as noted in Table 4 and Figure 2. Please refer to Appendix 1 for detailed information by country.

[†] Type I is a borosilicate glass with good chemical resistance. It is used for pharmaceuticals requiring the least reactive containers. Typical products include tubular glass vials, pre-fill syringes, cartridges, and ampules for small-volume parenterals and diagnostic reagents. Adelph Healthcare Packaging: http://www.adelphi-hp.com/information-centre/technical-information/pharmaceutical-glass-types?lang=en.

[‡] United States Pharmacopeial Convention. <661> Containers—Plastic: https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c661.pdf.

[§] SpillTech. Chemical Compatibility Guide For Polyethylene Items: https://www.spilltech.com/wcsstore/SpillTechUSCatalogAssetStore/Attachment/documents/ccg/POLYETHYLENE.pdf.

Table 4. Number of countries in sub-Saharan Africa and South Asia that list $MgSO_4$ on their NEML

	Number of countries			Number of countries of 18 whose NEML lists $MgSO_4$ as treatment for PE/E			
					NEML lists concentration		
	Developing countries in the region	NEML is available on WHO website	NEML includes $MgSO_4$ as treatment* for PE/E	NEML lists a specific primary container	50%	50% with other strengths	20% alone or with other strengths
Sub-Saharan Africa	48	28	18	4	14	1	1
South Asia	8	8	5	2	4	0	0

*Indication for use also includes anticonvulsant and antiepileptic.

Sub-Saharan Africa

The World Bank defines 48 countries in sub-Saharan Africa as having developing economies. Of the 48 developing economies, WHO has NEMLs available for 28 of those countries, 18 of which list $MgSO_4$ as an anticonvulsant, an antiepileptic, or treatment for PE/E. The remaining ten countries list $MgSO_4$ in their NEML but do not specify its intended use or list it for other indications, such as for treatment of hypertension, correction of electrolyte imbalances, laxative, or other.

Figure 2. Map of sub-Saharan African and South Asian countries that list $MgSO_4$ in their NEML, as posted on the WHO website.

Of the 18 countries that list $MgSO_4$ as an anticonvulsant or antiepileptic, or treatment for PE/E:

- Only five countries specify a primary container for $MgSO_4$, and all of them list an ampule as being the primary container.
- A total of 17 list strengths (concentrations) of $MgSO_4$, while one country does not specify it.
- 50% is the most common strength listed.
  - In all, 14 countries list 50% alone; one country lists 50% along with other strengths.
  - Two countries list 15% alone or list it along with another strength.
  - No country lists 20% alone; one country lists 20% along with other strengths, including 50%.

South Asia

The World Bank defines eight countries in South Asia as having developing economies, and WHO has NEMLs available for all of them. All eight countries list $MgSO_4$, and five of the eight list it for the treatment and prevention of PE/E.

Of the five countries that list $MgSO_4$ for the treatment and prevention of PE/E:

- Only two countries specify a primary container for $MgSO_4$, and both of them list an ampule as being the primary container.
- Five countries list the strengths (concentrations) of $MgSO_4$, and all five countries list a single strength.
- 50% strength is predominantly specified.
  - Four countries list 50%; one country lists 40%.
  - No country lists 20%.

Commercial feasibility: Cost and other implications for manufacturing

We contacted a few manufacturers directly and a few others indirectly with support from international procurement agencies. Most declined to talk with us; however, we did talk with one of the largest manufacturers of $MgSO_4$ solution. This manufacturer typically responds to government tenders and currently distributes its products to Kenya, Tanzania, and Uganda. It is now working with the Nigerian authority to enter that country's market. This manufacturer also supplies its products to nonprofit organizations. It produces a 50% $MgSO_4$ solution in ampules but does not produce a 20% $MgSO_4$ solution.

Our major findings are as follows:

- We confirmed that 75mL is not a standard size for glass containers; 50mL and 100mL glass containers are standard, although these are considered to be quite large. A small venting needle could be used as a way to release pressure while adding diluent, which would enable use of a smaller container. Even though this might impair the sterility of the $MgSO_4$ solution, it might not be a significant concern if the $MgSO_4$ solution were used immediately after dilution. Also, using venting needles is not significantly different from reconstituting freeze-dried injectable drugs.
- Although our desk research found that polylefin plastic polymers are compatible with $MgSO_4$, they are uncommon and would be expensive. They would also require a bespoke (i.e., custom) supply chain and most likely require considerable time to modify the manufacturing line, since this manufacturer currently uses only glass ampules for its $MgSO_4$ solution. We need to further investigate cost and benefits of polymer containers if we were proceed with $MgSO_4$ dilution bottle.
- The fill line could be incorporated into a label on the bottle (an ink line). If the fill line were printed or embossed directly on the bottle, the label would cover and conceal part of it.
- WFI is normally supplied in 10mL volumes. If 15mL of WFI needs to be added to the $MgSO_4$ dilution bottle, two ampules of WFI would be required, and 5mL would be wasted. In addition, there might be risk of contamination since the same needle would be used to withdraw WFI from the 10mL container and add it to the $MgSO_4$ dilution bottle. This step must be repeated twice. In order to avoid the wastage and risk of contamination, a 15mL ampule could be used for WFI, which would also eliminate the need for a fill line.
- The rubber septum (stopper) is easy to procure.
- The timeline for commercialization would be 9-12 months, depending on whether and what regulatory approval is required for the $MgSO_4$ dilution bottle. This timeline includes adjusting/adding a filling line, producing three validation batches, conducting a six-month stability test (given that shipments would be made to climate zone III [hot and dry] or IV [hot and humid]), and preparing a dossier for submission to the regulatory authority.
- Pricing-related information:
  - 10mL of 20% or 50% $MgSO_4$ would be between US$1.57 and $2.36.
  - A stopper would be approximately US$0.09 to 0.12.
  - A bottle or vial would cost 10-15 times more than an ampule. Therefore, many users would want to buy pharmaceuticals at the correct concentration in an ampule.

User acceptability: Concept testing with users

Two different dilution bottles were evaluated to be included in the ready-to-use packs. The sample size in each country is described in the tables below. The ministries of health in both countries identified regions and higher-level facilities where $MgSO_4$ was in use. PATH country staff in Ethiopia and Uganda invited health care workers who used $MgSO_4$ to participate in the FGDs and explained the purpose of the research. Those who attended the discussions were given a written consent form to ensure they understood the purpose of the study and had the opportunity to opt out.

Table 1. Focus group discussions (FGDs)

Country	Location	Participant type	No. of FGDs	No. of participants
Ethiopia	Urban hospital (Addis Ababa)	Midwives	1	6
	Periurban hospital (Mekele)	Midwives	1	6
	Periurban hospital	Ob/Gyns	1	2
	Rural health center (Tigray)	Midwives	1	6
		Subtotal	4	20
Uganda	Urban (Kampala)	Midwives	1	8
	Urban	Ob/Gyns	1	8
	Periurban (Jinja)	Midwives	1	13
		Subtotal	3	29
		Total	7	49

Table 2. In-depth interviews

Country	Decision-makers and procurement experts	No. of participants
Ethiopia	Ethiopian Midwives Association Pharmaceutical supply	2
Uganda	Ministry of Health senior officials Professor, Ob/Gyn Midwifery expert National Medical Stores Pharmacy	6
	Total	8

Although the two pack options that include two different types of dilution bottles were considered to be improvements over current practices, the bottles themselves were viewed as not offering significant benefit for the following reasons:

- Multiple steps still would be required for dilution, and these steps were regarded as being as complex and time consuming as current practices.
- Both types of dilution bottles would end up with some unused amount, and focus group participants and experts were concerned about wastage.
- A few people expressed concern that some health care workers might mistakenly withdraw the wrong amount or mistakenly administer the unused amount of $MgSO_4$ in the dilution bottle to another patient later on.
- Some thought that people might overfill the dilution bottle, even if it had a pre-marked fill line. One Ob/Gyn mentioned that having the fill line would encourage health care professionals to automatically fill the bottle with diluent, instead of deliberately diluting $MgSO_4$. This might, in turn, result in careless mistakes.
- In Uganda, health care workers already know they must administer 14g of $MgSO_4$ for women with PE/E (4g for IV and 10g for intramuscular [IM] injections). Therefore, diluting 10mL of 50% $MgSO_4$ solution to make 25mL of 20% solution would not be intuitive for them.

Only procurement personnel provided positive comments about the dilution bottle. They liked pack option 2 with the dilution bottle because only one type of bottle would need to be procured for both the loading and maintenance doses and for both IV and IM injections. This would reduce complexity in procurement and supply chain management. Please refer to PATH's report on the $MgSO_4$ ready-to-use pack field evaluation results for detailed information[**].

[**] PATH. *Magnesium Sulfate Ready-to-Use Pak. Results of Field Evaluation*.2015. Available at: http://www.lifesavingcommodities.org/wp-content/uploads/2015/06/Final-Report-MgSO4-Ready-to-use-pack_2015May28_final-4.pdf

Conclusion

The NEML review confirmed that sub-Saharan African and South Asian countries most commonly list 50% $MgSO_4$ as an anticonvulsant, an antiepileptic, or treatment for PE/E. In addition, this review confirmed that only a few countries specify the precise type of primary container. Since our concept dilution bottle would contain a 50% concentration of $MgSO_4$ for treatment of PE/E, it is unlikely that any of the current NEMLs present a significant hurdle for introduction of a dilution bottle for $MgSO_4$.

However, our desk research and the interview with one manufacturer confirmed that a 75mL bottle, the minimum size required for the $MgSO_4$ dilution bottle, is a non-standard size in the pharmaceutical industry. This manufacturer indicated that producing a non-standard bottle size could have implications for production cost and time to market, since manufacturers would need to identify a source for the non-standard size bottles, modify their production lines, and then obtain regulatory approval.

The materials used for the bottles also present some challenges. Although Type I glass is common and readily available, ease of distribution could be an issue due to the size and weight, especially considering the large size required for the dilution bottles. Polyolefin polymers could alleviate this issue and they are also compatible with $MgSO_4$. However, plastics are considered to be unique for bottle containers and costs could be high.

Our field evaluation of the dilution bottle concept furthermore revealed that health care professionals do not appreciate the value of the dilution bottle as much as we had expected. Consequently, we recommend not proceeding with the development of a dilution bottle.

It is noteworthy that this same field evaluation confirmed that health care professionals actually would prefer having a 20% $MgSO_4$ solution, since such a solution would obviate potential mistakes in dilution and would facilitate timely treatment of women with PE/E. Unfortunately, our NEML review ascertained that a 20% concentration of $MgSO_4$ is rarely listed on NEMLs. Changing NEMLs to include a 20% $MgSO_4$ solution would require substantial time and effort. Also, it would be difficult to incentivize manufacturers to produce and supply a 20% $MgSO_4$ solution, since the market size for this critical medicine remains relatively small.

This problem does not appear to have an easy solution. The most important factor to consider is whether the impact of not having a 20% $MgSO_4$ solution is significant or not. If not having a 20% $MgSO_4$ solution leads to serious adverse events, such as loss of life due to non-timely or improper treatment, then the cost and effort of changing NEMLs as well as financially motivating manufacturers to produce a 20% $MgSO_4$ solution might be justified. In addition, we should consider providing alternatives for a 20% $MgSO_4$ solution, such as a simplified regimen, that does not require health care professionals to dilute at the time of administration.

Appendix 1. Status of $MgSO_4$ listings on national Essential Medicines Lists in sub-Saharan Africa and South Asia

(http://www.who.int/selection_medicines/country_lists/en/)

Sub-Saharan Africa						
	Country	Gross National Income	$MgSO_4$ on NEML	Strengths	Anti-convulsant	Container for injectable $MgSO_4$
1	Benin	Low				
2	Burkina Faso	Low	✓	50%	✓	Ampule
3	Burundi	Low				
4	Central African Republic	Low				
5	Chad	Low	✓	1%, 15%	✓	Ampule
6	Comoros	Low				
7	Democratic Republic of Congo	Low	✓	50%	✓	Ampule
8	Eritrea	Low	✓	50%	✓	Ampule
9	Ethiopia	Low	✓	2%, 5%, 10%, 20%, 50%	Other	-
10	The Gambia	Low				
11	Guinea	Low	✓	-	-*	-
12	Guinea-Bissau	Low				
13	Kenya	Low	✓	50%	✓	-
14	Liberia	Low				
15	Madagascar	Low	✓	15%	Other	-
16	Malawi	Low				
17	Mali	Low	✓	50%	✓	-
18	Mozambique	Low				
19	Niger	Low				
20	Rwanda	Low	✓	50%	✓	-
21	Sierra Leone	Low				
22	Somalia	Low	✓	50%	-	-
23	Tanzania	Low	✓	50%	✓	-
24	Togo	Low	✓	50%	✓	-
25	Uganda	Low	✓	50%	✓	-
26	Zimbabwe	Low	✓	-	✓	-
27	Cameroon	Low-middle	✓	-	Other	-
28	Cabo Verde	Low-middle	✓	20%, 50%	Other	Ampule
29	Republic of Congo	Low-middle	✓	15%	✓	-
30	Cote d'Ivoire	Low-middle				
31	Djibouti	Low-middle	✓	15%, 50%	Other	-
32	Ghana	Low-middle	✓	20%, 25%, 50%	✓	-

Sub-Saharan Africa						
	Country	Gross National Income	$MgSO_4$ on NEML	Strengths	Anti-convulsant	Container for injectable $MgSO_4$
33	Lesotho	Low-middle	✓	50%	Other	-
34	Mauritania	Low-middle				
35	Nigeria	Low-middle	✓	50%	✓	-
36	São Tomé and Principe	Low-middle				
37	Senegal	Low-middle				
38	South Sudan	Low-middle				
39	Sudan	Low-middle	✓	-	Other	-
40	Swaziland	Low-middle				
41	Zambia	Low-middle	✓	50%	✓	-
42	Angola	Upper-middle				
43	Botswana	Upper-middle	✓	50%	✓	-
44	Gabon	Upper-middle				
45	Mauritius	Upper-middle				
46	Namibia	Upper-middle	✓	50%	-	-
47	Seychelles	Upper-middle	✓	50%	✓	-
48	South Africa	Upper-middle	✓	50%	✓	-

*Included in National Therapeutic Guide for the treatment of severe preeclampsia

	No information on NEML
✓	Listed/specified on NEML
-	Not specified
Other	Indications for use other than anti-convulsant

South Asia						
	Country	Gross National Income	NEML	Strengths	Anti-convulsant	Container for injectable $MgSO_4$
1	Afghanistan	Low	✓	50%	✓	Ampule
2	Bangladesh	Low	✓	-	-	-
3	Nepal	Low	✓	50%	✓	-
4	Bhutan	Low-middle	✓	50%	-	-
5	India	Low-middle	✓	50%	✓	-
6	Pakistan	Low-middle	✓	50%	✓	Ampule
7	Sri Lanka	Low-middle	✓	40%	✓	-
8	Maldives	Upper-middle	✓	25%, 50%	-	-

✓	Listed/specified on NEML
-	Not specified